REMARKS

Reconsideration is requested.

Claims 9, 14 and 21 have been canceled, without prejudice. Claims 1-8, 10-13, 15-20 and 22-50 are pending. Claims 32-50 have been withdrawn from consideration. The above amendments have been made to correct certain informalities noted by the Examiner in the Office Action of May 13, 2004 and to make claim 31 consistent with pending claim 1 in the description of the biological sensing element. The amendments are not believed to introduce new matter or require further search and/or consideration. Entry of the amendments will, at a minimum, reduce the issues for appeal by obviating at least the claim objections noted below. Entry of the above amendments is requested.

Entry of the above amendments and consideration of the following remarks, are requested.

The formalities indicated by the Examiner in ¶2. of the Office Action dated May 13, 2004, have been corrected above.

The claim objections noted in ¶3. of the Office Action dated May 13, 2004 have been obviated by the above amendments. The Examiner's consideration of the noted dependent claims in the Office Action of May 13, 2004, is acknowledged, with appreciation.

The Section 102 rejection of Claims 1-5, 10, 13-14, 20, 25-26 and 28-31 over Reed (U.S. Patent No. 6,492,143), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

According to ¶6. of the Office Action dated May 13, 2004, the applicants understand that the Examiner believes Reed (a) to define receptors "discretely

immobilised onto or within a solid support" and (b) that the receptors of Reed have attached thereto a detectable label. The Examiner is requested to correct any error in the applicants understanding of the Examiner's position.

The applicants believe that Reed describes suspensions of cells in liquid media measured in sequence rather than simultaneously as an array. The sensing element in the case of Reed is believed to be an entire and functional cell, whose physiology is changed by the binding of odorant molecules. The sensing elements of Reed are further understood to be attached to a detectable label - however, this label undergoes no change on ligand binding and exists to enable the localization of the proteins in the cells. Furthermore, the cells, which may be, for the sake of argument only, equivalent to the sensing elements of the present invention, are not immobilized however, such as in a microtiter plate, but rather are in liquid suspension on a microscopic slide.

The Examiner is understood to rely on column 34 of Reed, at lines 62-65 for the first aspect of the basis for the rejection stated above. It is noted that the section of Reed starting at column 34, line 56 is concerned with the "Identification of Cognate Ligand-receptor Pairs for the Cloned Receptor Library" and that, in this method, plasmid clones are arrayed in microtiter plates. The Examiner is understood to believe that the sensing elements are the clones expressing TM II-IV receptor – however the applicants believe that a more complete review of the paragraph bridging columns 34 and 35 of the cited reference shows that the plasmid clones are transfected into HEK-293 cells and that it is the transfected cells that were screened against odorants. The sensing element in this example of the cited art is, therefore, the transfected cell itself.

This is in contrast with the presently claimed invention, such as is defined in claim 1, which clearly states that the biological sensing element is a polypeptide or a fragment, truncation, domain or concatenation thereof comprising at least a ligand binding site of the polypeptide. In the present invention, it is the polypeptide or fragment, truncation, domain or concatenation thereof which is discretely immobilised onto or within a solid support.

Yet a further difference between the disclosure of Reed and the presently claimed invention is the lack of immobilization of the sensing element in Reed. Claim 1 of the present application, for example, states that the biological sensing element is "discretely immobilized onto or within a solid support". As detailed above, the sensing element of Reed, i.e., the cell, is in liquid suspension on a microscopic slide and hence is not immobilized, as required by the present claims.

The transfected cell of Reed as sensing element does not anticipate the polypeptide or fragment, truncation, domain or concatenation thereof as sensing element in the presently claimed invention.

The Examiner is understood to further rely on, for example, column 33, lines 4-48 of Reed for the second basis of the Section 102 rejection noted above. This aspect of Reed is understood to describe the expression within HEK-293 cells of the TM II-IV region from the β2-adrenergic receptor together with a rhodopsin tag. This tag is detectable using the B6-30 antibody.

However, claim 1 of the present application, for example, specifies that the sensing element has attached thereto a detectable label. As discussed above, the sensing element of the Reed construct is the HEK-293 cell itself. There is nothing in the

Reed disclosure that teaches the labeling of the cell *per se* and hence the applicants believe that Reed fails to anticipate the presently claimed invention.

For completeness, the applicants note that the label of Reed is used for "immunocyto-chemical localization" [col 33, line 7] as opposed to detection of ligand binding wherein, as specified in claim 20 of the present application, the detectable label is susceptible to change upon ligand binding.

It is furthermore noted that claim 1 of the present application, for example, requires that the array comprises one or more groups of broad specificity biological sensing elements and variants thereof. The cell expression system of Reed requires the biological sensing element to be the whole cell itself (as discussed above) and there is no teaching or suggestion of any variants of the cell as sensing element.

The applicants submit that it is apparent, therefore, (i) that the construct of Reed does not contain each and every component of the construct of the presently claimed invention and (ii) those components of the construct of Reed are different from the "equivalent" components of the construct of the presently claimed invention.

The claims are submitted to be patentable over Reed.

Regarding present claims 2 and 3, the Examiner is understood to suggest that Reed discloses a detector wherein there is at least one group (with respect to claim 2) and from 2 to 50 groups (with respect to claim 3). It is noted, however, that claim 1 of the present application, upon which claims 2 and 3 are dependent, specifies that a "group" is of a broad specificity biological sensing element and variants thereof. As previously stated, the sensing element of Reed is understood to be the cell *per se* and Reed does not describe variants of the cell *per se*, but rather, at best, only of the DNA

sequences encoding the TM II-IV receptor. Thus, claims 2 and 3 are submitted to not be anticipated by Reed.

Regarding present claims 4 and 5, the Examiner is understood to suggest that Reed discloses a group consisting of a biological sensing element and from 1 to 100 and from 5 to 25 variants respectively. The applicants respectfully disagree with the Examiner's interpretation of the cited art. As discussed above, a "group" is of a broad specificity biological sensing element and variants thereof. The sensing element of Reed is the cell *per se* and Reed does not describe variants of the cell *per se*, but rather, at best, only the DNA sequences encoding the TM II-IV receptor. Thus, claims 4 and 5 are not submitted to be novel over Reed.

Regarding claim 10, the Examiner is understood to believe that Col 23, lines 5-11 and 39-44 and Col 24, lines 5-9 and 38-42 of the cited art describe a ligand binding site containing one or more cysteine residues. The applicants urge the Examiner to appreciate however that in the present application it is the biological sensing element that comprises a ligand binding site and that the biological sensing element is specified in claim 1, for example, to be a polypeptide or a fragment, truncation, domain or concatenation thereof. As discussed above, the sensing element of Reed is the cell *per se*. The cell *per se* as biological sensing element may comprise a protein comprising a ligand binding site comprising one or more cysteine residues – however, the cell itself as biological sensing element does not contain one or more cysteine residues. Hence claim 10 is further submitted to be novel over Reed.

In respect of claim 13, the Examiner is understood to believe that the claim is anticipated by Reed at column 34-35. Claim 13 specifies that the variant is derived from

a biological sensing element and differs therefrom in its binding specificity and/or affinity. At the section of Reed highlighted by the Examiner, the biological sensing element is the transfected HEK-293 cell, as discussed above, and the "variants" are the 'various odorant' defined on line 60 of column 24. As there is no identity between the variant of the present application and the variant of Reed, Reed is not believed to anticipate the present claims.

Claim 14 has been canceled, without prejudice.

Claim 20 is understood to have been rejected as allegedly being additionally anticipated by the disclosure of column 33, line 28 onwards of Reed. However, the rhodopsin label referred to at this reference is not believed to change upon ligand binding. The Ca2+ dependent signal described is generated through changes in the cell membrane affecting internal cell Ca2+ concentration caused by receptor binding proteins interaction with odorant molecules. These changes affect the fluorescence of FURA-2 and in no way rely on the presence of the rhodopsin label.

The rejection of claims 25 and 26 is, with due respect, submitted to be improper. Reed discloses the fluorophore as a method of localizing the binding protein in a cell. This is a method for confirming that proteins are being expressed in particular cell cultures and does not relate to protein activity, as in the presently claimed invention. This does not form part of the detection process of odorant binding.

Regarding claims 28, 29 and 30, the Examiner is understood to state that Reed discloses the detector where the sensing element is an odorant binding protein, preferably a mammalian odorant binding protein and more preferably a human odorant binding protein. As is discussed above, the applicants believe that Reed does not

describe an array where the sensing element is an odorant binding protein. On the contrary, the sensing element of Reed is a cell and Reed discloses the use of cells expressing binding proteins as a means of measuring the binding of odorant molecules to binding proteins expressed by the cell as sensing element. The sensing element, i.e. the mechanism by which binding is detected, is the whole cell.

Claim 31 specifies that the biological sensing element is a polypeptide or fragment, truncation, domain or concatenation thereof, as in present claim 1. The comments above with regard to the patetability of claim 1 over Reed equally apply therefore to Claim 31.

The claims are submitted to be patentable over Reed and withdrawal of the Section 102 rejection based on the same is requested.

The Section 102 rejection of Claims 6-8 over Reed "as defined by" Dal Monte et al (Chemical Senses, 1993, 18 (6): 713-721), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above distinguishing aspects of the claimed invention over Reed. As submitted above, Reed does not anticipate, for example, independent claim 1 of the application, upon which claims 6 to 8 depend. Therefore defining Reed by Dal Monte is not believed to further anticipate the noted dependent claims and withdrawal of the Section 102 rejection of claims 6-8 is requested.

The Section 103 rejection of Claims 11-12, 15-19, 22-24 over Reed in view of Hoffman (U.S. Patent No. 5,998,588), is traversed. Reconsideration and withdrawal of the Section 103 rejection are requested in view of the following distinguishing remarks.

The deficiencies of Reed noted above are not believed to be cured by the cited Hoffman document.

As submitted above, significant differences exist between the teaching of Reed and the presently claimed invention. Moreover, the applicants submit that combination of Reed with the disclosure of Hoffman, even if one of ordinary skill in the art were motivated by the art to make such a combination, would not have resulted in the presently claimed invention.

The disclosure of Reed is concerned with the provision of novel libraries of nucleic acids encoding odorant/ligand-binding domains. Test methods are described (col 4, lines 48-56) for determining whether a test compound binds to a mammalian olfactory receptor but, in this method, as described in column 33 of Reed, as discussed above, a HEK 293 cell is transfected with the nucleic acid encoding the olfactory receptor, the transfected cell is placed in solution and contacted with the test compound and any binding is measured by determination of changes in Ca2+ levels. Different cells may be transfected with different nucleic acid sequences, but measurement is always sequential and not simultaneous, such that the method of Reed does not involve the use of an array, as defined, for example, in the presently claimed invention.

Hoffman discloses inserting cysteine residues into amino acid sequences to enable the binding of molecules to specific sites within a protein sequence to allow their subsequent manipulation. However, as specified at col 16, lines 10-58 of Hoffman, the binding of molecules is described that should ".. not adversely affect the enzyme activity .." to a target protein. This specifically teaches that the insertion of cysteine and the subsequent binding of molecules should not affect binding specificity.

The molecules bound to proteins in Hoffman are used to manipulate the structure and therefore binding behavior of the protein through introduction of external stimuli. e.g. light, pH or temperature. This is done to produce binding proteins which have effectively "switchable" binding affinities.

The ordinarily skilled person would not have been motivated to combine the disclosure of Hoffman with that of Reed. As stated above, Reed describes a cell-based assay in which the entire cell is the sensing element. Hoffman teaches the insertion of cysteine residues to manipulate structure and therefore binding behavior via external stimuli. Modification of the entire cell as sensing element of Reed by insertion of a cysteine residue as per Hoffman is not believed to be a logical or expected result one of ordinary skill in the art would be motivated to make. Moreover, the applicants believe that one of ordinary skill in the art would find such a combination an unpredictable task which one of ordinary skill would believe may require an undue amount of experimentation. Further, the applicants believe that combination of the disclosure of these two documents would not have resulted in the invention of the present disclosure which teaches an array comprising a polypeptide as sensing element in which the ligand binding site can be modified by insertion of cysteine residues.

The applicants further submit that introduction of cysteine residues as per Hoffman would not advance the system of Reed as Reed does not disclose the attachment of a detectable label to the sensing element. As discussed above, the sensing element of Reed is the cell *per se* and the label in Reed col 33 (rhodopsin tag) is co-translated with the translated receptor. As discussed above, the rhodopsin tag is not a detectable label but rather is present to cause translocation of the translated

receptor to the cell membrane whereby the presence of the translated receptor results in a detectable change. Thus, even if the ordinarily skilled person found some way to add cysteine residues to the translated receptor of Reed, which is not expected, the resulting construct would still not have rendered the array of the present application obvious as the sensing element, i.e., the cell, of Reed does not itself contain a detectable label.

In view of all of the above therefore, the applicants submit that the claims are patentable over the combination of the cited Reed and Hoffman references and withdrawal of the Section 103 rejection based on the same is requested.

The Section 103 rejection of claim 27 over Reed in view of Gold (U.S. Patent No. 6,242,246), is traversed. Reconsideration and withdrawal of the Section 103 rejection are requested in view of the following distinguishing remarks.

The deficiencies of Reed noted above are not cured by Gold.

Claim 27 is submitted to be patentable over Reed in view of Gold. As discussed above, the label described in Reed is not a detectable label but rather is a tag causing membrane translocation. This label may be used to determine localization of the translated polypeptide, but, in that case, it is a detectable antibody (col 33) that is used to bind to the rhodopsin tag. Thus, even if the ordinarily skilled person were to consider using the fluorescent probes described in Gold in the system of Reed, which the applicants do not concede would be motivated by the cited art, there is nothing in Reed that teaches the attachment of a detectable label to the cell, being the sensing element of Reed.

In view of this, therefore, it is submitted that claim 27 is inventive over Reed and Gold and withdrawal of the Section 103 rejection of claim 27 is requested..

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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